REMARKS

Reconsideration and allowance are respectfully requested.

Claims 1, 3-14 and 18-29 are pending. The amendments are fully supported by the original disclosure and, thus, no new matter is added by their entry. Support may be found, inter alia, at page 3, lines 19-20; page 4, lines 11-13; and page 6, lines 27-30, of the specification.

35 U.S.C. 103 – Nonobviousness

A claimed invention is unpatentable if the differences between it and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art. *In re Kahn*, 78 USPQ2d 1329, 1334 (Fed. Cir. 2006) citing *Graham v. John Deere*, 148 USPQ 459 (1966). The *Graham* analysis needs to be made explicitly. *KSR v. Teleflex*, 82 USPQ2d 1385, 1396 (2007). It requires findings of fact and a rational basis for combining the prior art disclosures to produce the claimed invention. See id. ("Often, it will be necessary for a court to look to interrelated teachings of multiple patents . . . and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue"). The use of hindsight reasoning is impermissible. See id. at 1397 ("A factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon ex post reasoning"). Thus, a prima facie case of obviousness requires "some rationale, articulation, or reasoned basis to explain why the conclusion of obviousness is correct." *Kahn* at 1335; see *KSR* at 1396. An inquiry is required as to "whether the improvement is more than the predictable use of prior art elements according to their established functions." Id. at 1396. But a claim directed to a combination of prior art elements "is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." Id. Finally, a determination of prima facie obviousness requires a reasonable expectation of success. See *In re Rinehart*, 189 USPQ 143, 148 (C.C.P.A. 1976).

Claims 1, 3-13 and 18-28 were rejected under Section 103(a) as allegedly unpatentable over Goldenberg et al. (U.S. Patent Publ. 2001/0006618) in view of Cokgor et al. (J. Clin. Oncol. 18:3862-3872, 2000). Applicants traverse.

Cokgor administered radiolabeled antibody by direct injection into spontaneous cysts, into surgically created resection cavities (SCRCs), intrathecally, and into tumors. But delivering a single dose of radiation directly to the tumor, exposed during surgery, or to the anatomical area that contained the tumor after surgical removal of the cancer is disadvantageous because such procedures are logistically complicated and expensive: only a few primary treatment centers have the necessary expertise to implement this type of therapy; the cost of the equipment alone is several million dollars (without even considering the construction costs for building a shielded operating theater to ensure radioprotection for the operators and people in the adjacent rooms), and the specialist staff necessary for implementing the treatment. See page 2, first paragraph, of Applicants' specification.

The intravenous inoculation of the labeled antibody as disclosed in Goldenberg does not present the disadvantages described above, but only s modest amount of antibodies and proteins of the avidin family reach the target after inoculation. See page 3, first paragraph, of Applicants' specification. Also Cokgor teaches that systemically administered radiolabeled monoclonal antibodies (mAbs) have not been effective in the treatment of brain tumors because (1) only small amounts of mAb will cross the blood-brain barrier, (2) there is high interstitial fluid pressure in tumors and surrounding normal tissue, (3) mAb lacks specificity and have less than optimal binding affinity, and (4) the catabolism of radioactive label. The aforementioned are explicit teachings away from combining Goldenberg and Cokgor as proposed in the Office Action.

The present invention, which includes a first intraoperative locoregional step and a second postoperative systemic step, solves the problem of delivering the anticancer agent directly to the tumor and avoids the disadvantages mentioned above. The administration, during surgery, of an agent endowed with tumor tropism (i.e., capable of concentrating locally on the tumor or in the vicinity of it), immediately prepares, in the residual tissue around the tumor, a sort of receptor of our choosing ready to attract, locally

and in an extremely high concentration, the subsequent dose of actual anticancer agent administered intravenously. Applicants' claimed method avoids the problem of handling an anticancer agent, in particular a radioactive anticancer agent, in accordance with the prior art.

The immediate advantage brought about by the present invention, namely in the increased accumulation of the agent endowed with tumor tropism reduces the amount of anticancer agent used. See page 4, second paragraph, of Applicants' specification. On page 8, first paragraph, of the present specification, it is taught that, for (DOTA)-^{90}Y/^{177}Lu biotin administered intravenously, the initial activity will be 50 mCi for ^{90}Y and 80 mCi for ^{177}Lu. On the basis of previous experience with radioimmunotherapy, these activities are 1/3 less than the maximum activity that can be administered per cycle. This reduction was not predictable and represents a considerable advantage provided by the present invention.

In the present amendments, this limitation is inserted into the independent claims (see claims 1, 18 and 23) and emphasizes the use of a first agent which is capable of concentrating locally on the tumor or in the vicinity of it, there is increased accumulation of the first agent in the tumor site which permits reduction in the amount of the second anticancer agent to be administered.

A further advantage of the present invention, as compared to radioimmunotherapy in general, is that it drastically reduces the time elapsing between removal of the primary tumor and subsequent adjuvant therapy. In fact, as taught on page 7, last paragrapht, of Applicants' specification, from a minimum of 4 hours to 2-3 days postoperatively, the patient will be accompanied to the nuclear medicine department to start the postoperative therapeutic step with radiolabeled biotin administered systemically. In particular, comparing the present invention with Goldenberg, one of ordinary skill in the art would distinguish, in Goldenberg's teachings, between detection methods and therapeutic methods. Referring to the method of treating tumors, which is the objective of the present invention, Goldenberg teaches a three-step biotin-avidin procedure that takes from 2 to 11 days (see paragraph [0062] at pages 5-6).

Moreover, the method of the present invention is particularly advantageous in controlling local recurrences, and, surprisingly, it has been seen that local therapy can be advantageously administered in only two steps, the first of which is performed intra-operatively in a locoregional site and the second postoperatively via a systemic route. See page 3, first paragraph, of Applicants' specification of the Summary of Invention.

Another advantage not taught in the prior art is that, to achieve maximum biotinylated antibody accumulation capacity in the target area, a mixture of biotinylated monoclonal antibodies, which are directed against different tumor antigens or against proteins of the extracellular matrix, can be used. See page 5, third paragraph, of Applicants' specification.

None of the abovementioned advantages are taught or suggested by combining Goldenberg's first composition with Cokgor's local administration followed at a later time by parenteral administration of the second composition as taught by Goldenberg. In particular, one of ordinary skill in the art would not have expected a reduction in the dose of radiolabeled anticancer agent. This advantage represents a critical improvement in the treatment of tumors because it does not reduce therapy efficacy, but brings important benefits not only to the patient in terms of reducing side effects due to the radioactive anticancer drug, but also to medical personnel in terms of safety. Also, one of ordinary skill in the art would not have expected the reduction in treatment time. Also without reducing the efficacy of treatment, there is the benefit of increased compliance by the patient.

Moreover, the Examiner's citation of Goldenberg's paragraph [0023] is not relevant to Applicants' claimed invention because that passage refers to "non-malignant pathological lesions" and thus, one of ordinary skill in the art would not consider it pertinent to a method of treating patients with a solid tumor.

Withdrawal of the Section 103 rejection is requested because the claims would not have been obvious to one of ordinarily skill in the art when this invention was made.

Conclusion

Having fully responded to the pending Office Action, Applicants submit that the claims are in condition for allowance and earnestly solicit an early Notice to that effect. The Examiner is invited to contact the undersigned if any further information is required

Respectfully submitted,

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